USPQ2d 1738, 1990). In this case, the court reviewed patentability of claims directed to methods for using aminoorganosilane compounds. As noted by the appellate panel, the PTO had previously determined (in a parent application to the divisional case on review) that the subject aminoorganosilane compounds themselves were patentable. However, the PTO had refused to allow claims in the divisional application to methods for using the patentable compounds (even though the divisional case was filed pursuant to a Restriction Requirement entered by the Examiner in the parent case). The Federal Circuit reversed the PTO's decision--holding that the divisional method claims were clearly patentable. In reaching its conclusion, the court held that:

> From the standpoint of patent law, a compound and all of its properties are inseparable, they are one and the same thing....The compounds and their use are but different aspects of, or ways of looking at, the same invention and consequently that invention is capable of being claimed both as new compounds or as a new method or process of bonding/priming. [*Id.* at 1741]

The court further explained that:

> In the present case likewise, §103 obviousness...depends on the obviousness of using appellant's new compounds, which constitute the essential limitations of the claims, in light of the prior art. That being so, the board's hindsight comparison of the functioning of the new compounds with the functioning of the compounds of the prior art was legal error. It uses appellant's specification teaching as though it were prior art in order to make claims to methods of bonding/priming using his *admittedly novel compounds* appear to be obvious. We hold that appellant is entitled to his method of use claims.... [*Id.* at 1742, *emphasis added*]

This long-standing authority applies directly to the facts presented in the instant application. As a result of a Restriction Requirement imposed by the Office, Applicants were compelled to prosecute compound claims directed to their novel (-)-1-(3,4-dlchlorophenyl)-3-azabicyclo[3.1.0]hexanes in separate applications from Applicants' novel methods for use employing these compounds. Applicants' compound claims, directed to (-)-1-(3,4-dlchlorophenyl)-3-azabicyclo[3.1.0]hexanes, have been previously examined and determined by the Office to be patentable (USPN 6,569,887). Additionally, the Office previously examined and allowed Applicants' distinct invention directed to generic methods for using (-)-1-(3,4-dlchlorophenyl)-3-azabicyclo[3.1.0]hexanes to treat disorders alleviated by inhibiting dopamine reuptake (USPN 6,716,868).

Considering these antecedent dispositions by the PTO, in light of the authority presented above, Applicants are clearly entitled to additional claims employing their novel and non-obvious (-)-1-(3, 4-dichlorophenyl)-3-azabicyclo[3.1.0]hexanes in the instantly-recited

methods. Notably, the claims presented in the instant application were compelled to be separately prosecuted herein pursuant to a Restriction Requirement levied by the Office in US Application Serial No. 10/425,545 (the parent case of the present application, which ultimately issued as US Patent No. 6,716,868). Accordingly, the rejection of claims 24, 26-29, 31-44 and 49-52 under 35 USC § 103(a) as allegedly unpatentable over Beer et al., US 6,204,284, is respectfully submitted to be overcome.

To further clarify the record in the instant application, Applicants wish to enter into the record additional data supportive of the instantly-claimed methods, which correlate with the data presented in the specification as filed. These data were obtained by Applicants using more sensitive model systems than described in the original disclosure to demonstrate unexpected functional differences between the racemic mixture of Beer et al. and the compounds of the present invention (i.e., which are "substantially free" of the (+) enantiomer). These more sensitive, confirmatory studies were performed comparing (-)-1-(3,4-dlchlorophenyl)-3-azabicyclo[3.1.0]hexane HCl, (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl in dopamine, norepinephrine, and serotonin transporter binding and uptake assays using recombinant human receptors. The details of these studies are set forth in Attachment A hereto.

Briefly, the follow-on studies presented in Attachment A evince that, in more sensitive model systems, (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl exhibits some detectable binding and uptake activity with respect to recombinant human serotonin and norepinephrine receptors. However, consistent with Applicant's original disclosure, this binding and uptake activity is significantly and unexpectedly low compared to that of (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl. These results correlate with the results set forth in Example 6 of the instant application obtained using a different model system. As a result, based on the original data in the disclosure, as further resolved by the follow-on studies presented in Attachment A hereto, the use of the (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl yields desirable and unexpected properties of preventing or reducing side effects associated with inhibiting norepinephrine uptake and serotonin uptake, such as hypertension and sexual dysfunction, respectively.

The foregoing comments further evince that the rejection of claims 25, 30, and 45-48 under 35 USC § 103(a) as allegedly unpatentable over Beer et al., US 6,204,284 is unsupported by the facts of record.

Double Patenting

The Advisory Action dated September 16, 2005 states that the "[i]nstant claims and claims in US '868 and 10/764,371 are substantial duplicates." On this basis, it appears that the rejection of claims in the present application under 35 U.S.C. § 101 as allegedly claiming the same invention of US Patent No. 6,716,868 and US Application Serial No. 10/764,371 is maintained.

The legal standard for double patenting is not whether claims are "substantial duplicates," as stated by the examiner. Rather, as set forth in the MPEP:

> Where the claims of an application are *substantively the same* as those of the first patent, they are barred under 35 U.S.C. 101-the statutory basis for a double patenting rejection....Thus, the term "same invention," in this context, means an invention drawn to *identical* subject matter. [MPEP § 8.04(II), citations omitted, *emphasis added*]

The MPEP further discusses a specific example of when a statutory double patenting rejection is not appropriate:

> Is there an embodiment of the invention that falls within the scope of one claim, but not the other? If there is such an embodiment, then identical subject matter is not defined by the claims and statutory double patenting would not exist. For example, the invention defined by a claim reciting a compound having a "halogen" substituent is not identical to or substantively the same as a claim reciting the same compound except having a "chlorine" substituent in place of the halogen because "halogen" is broader than 'chlorine.'" [MPEP § 8.04(II)(A)]

Based on this administrative authority, a statutory double patenting rejection in the instant case is clearly improper. The claims of the instant application are directed to methods for treating certain specific health disorders (attention deficit disorder, depression, obesity, Parkinson's disease and tic disorders). The claims of US Application Serial No. 10/764,371 are distinctly directed to methods for treating different health disorders (particularly, addictive disorders). The claims of US Patent No. 6,716,868 are generally directed to methods for treating or preventing disorders alleviated by inhibiting dopamine reuptake using (-)-1-(3, 4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, which is likewise distinct according to the MPEP authority noted above from the specific health disorders claimed in the instant application. Indisputably, the claims of the present application recite limitations that are not included in the claims of U.S. Patent No. 6,716,868 and US Application Serial No. 10/764,371. It is axiomatic then that the claims of the instant application are not "substantively the same" nor directed to identical subject matter as, the claims of either US Patent No. 6,716,868 nor US Application Serial No. 10/764,371.

Further clarifying this position with respect to US Patent No. 6,716,868, the MPEP cautions against confusing domination and double patenting as follows:

> Domination and double patenting should not be confused. They are two separate issues. One patent or application "dominates" a second patent or application when the first patent or application has a broad or generic claim which fully encompasses or reads on an invention defined in a narrower or more specific claim in another patent or application. Domination by itself...cannot support a double patenting rejection. [MPEP § 8.04(II), citations omitted]

In the present application, all claims are directed to the treatment of specific disorders (attention deficit disorder, depression, obesity, Parkinson's disease and tic disorders), and although these claims may be "dominated" by claims of US Patent No. 6,716,868, this cannot form a proper basis for a statutory double patent rejection.

Further evincing the improper nature of the Office's statutory double patenting rejection, Applicants note that the various claims presented in the instant application, in US Application Serial No. 10/764,371, and in US Patent No. 6,716,868, were compelled to be separately prosecuted by a Restriction Requirement levied by the Office in US Application Serial No. 10/425,545 (the parent case of the present application, which ultimately issued as US Patent No. 6,716,868). In this Restriction Requirement, claims generally directed to methods for treating or preventing disorders alleviated by inhibiting dopamine reuptake using (-)-1-(3, 4-dichlorophenyl)-3-azabicyclo[3.1.0]hexanes, and claims directed to the treatment of addictive disorders using these compounds, were expressly distinguished by the Office into different groups from the instantly-presented claims directed to the use of (-)-1-(3, 4-dichlorophenyl)-3-azabicyclo[3.1.0]hexanes to treat attention deficit disorder, depression, obesity, Parkinson's disease and tic disorders. Under these circumstances, a statutory double patenting rejection is facially improper. [*See*, 35 U.S.C. § 121; MPEP § 804.01]

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at (425) 455-5575.

Date: November 14, 2005

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Enclosures

ATTACHMENT A

ACTIVITY COMPARISON OF (-)-1-(3,4-DICHLOROPHENYL)-3-AZABICYCLO[3.1.0]HEXANE HCL, (+)-1-(3,4-DICHLOROPHENYL)-3-AZABICYCLO [3.1.0]HEXANE HCL AND (±)-1-(3,4-DICHLOROPHENYL)-3-AZABICYCLO[3.1.0]HEXANE HCL IN DOPAMINE, NOREPINEPHRINE, AND SEROTONIN TRANSPORTER BINDING AND UPTAKE ASSAYS USING RECOMBINANT HUMAN RECEPTORS

Dopamine, norepinephrine, and serotonin uptake-inhibition activity of (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane hydrochloride was compared to that of (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane hydrochloride and (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane hydrochloride using human cell lines transfected with cDNA molecules expressing recombinant human receptors.

I. MATERIALS AND METHODS

A. MATERIALS.

Radiolabeled neurotransmitters ([^{3}H]DA, [^{3}H]5-HT, [^{3}H]NE and [^{125}I]RTI-55) were purchased from NEN-Life Sciences (Boston, MA). Most other reagents were purchased from Sigma Chemical Co. (St. Louis, MO). The cloning and characterization of hDAT cDNA used in these experiments (pcDNA1-hDAT) was performed as described previously (Eshelman AJ *et al.*, Release of dopamine via the human transporter, *Mol. Pharmacol.* 45:312-316, 1994; Eshelman AJ *et al.*, Characterization of recombinant human dopamine in multiple cell lines, *J. Pharmacol. Exp. Ther.* 274:276-283 (1995). hSERT cells and HEK cells expressing the hNET (HEK-hNET) were provided according to previously-published methods (see, e.g., Ramamoorthy, S *et al.*, Antidepressant- and cocaine-sensitive human serotonin transporter: Molecular cloning, expression, and chromosomal localization, *Proc. Natl. Acad. Sci. USA* 90:2542-2546, 1993; and Galli A *et al.*, Sodium-dependent norepinephrine-induced currents in norepinephrine-transporter transfected HEK-293 cells blocked by cocaine and antidepressants, *J. Exp. Biol.* 198:2197-2212, 1995).

B. BINDING ASSAYS.

HEK-hDAT and HEK-hSERT cells were incubated in Dulbecco's modified Eagle's medium supplemented with 5% fetal bovine serum, 5% calf bovine serum, 0.05 U penicillin/streptomycin, and puromycin (2 μg/ml). HEK-hNET cells were incubated in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 0.05 U penicillin/streptomycin, and geneticin (300 μg/ml). Cells were grown until confluent on 150-

mm-diameter tissue culture dishes in a humidified 10% CO_2 environment at 37°C. Medium was removed from the plates, cells washed with 10 ml of PBS, lysis buffer (10 ml, 2 mM HEPES, 1 mM EDTA) was added, and plates were placed on ice for 10 min. Cells were scraped from plates and centrifuged for 20 min at 30,000*g*. The pellet was resuspended in 6 to 24 ml of 0.32 M sucrose with a Polytron homogenizer at setting 7 for 5 sec.

Assays contained an aliquot of membrane preparation (approximately 12-30 μg protein, depending on the cell line, which resulted in binding <10% of the total radioactivity), drug, [^{125}I]RTI-55 (40-80 pM final concentration) in a final volume of 250 μl. Krebs-HEPES assay buffer (25 mM HEPES, 122 mM NaCl, 5 mM KCl, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1 μM pargyline, 100 μM tropolone, 2 mg glucose/ml, 0.2 mg ascorbic acid/ml, pH 7.4) was used for all assays. Specific binding was defined as the difference in binding observed in the presence and absence of 5 μM mazindol (HEK-hDAT and –NET) or 5 μM imipramine (HEK-hSERT). Membranes were preincubated with drugs at room temperature for 10 min before the addition of [^{125}I]RTI-55, unless indicated otherwise. The reaction was incubated for 90 min at room temperature in the dark and was terminated by filtration through Wallace Filtermat A filters using a 96-well Tomtec cell harvester. Scintillation fluid (50 μl) was added to each filtered spot, and radioactivity remaining on the filter was determined using a Wallace 1205 Betaplate or 1405 microBeta scintillation counter. Competition experiments were conducted with duplicate determinations for each point.

C. INHIBITION OF RADIOLABELED NEUROTRANSMITTER UPTAKE IN HEK-HDAT, -HSERT AND –HNET CELLS.

Cells were grown on 150-mm-diameter tissue culture plates as described above. Medium was removed and plates were washed twice with Ca^{2+}, Mg^{2+}-free PBS. Fresh Ca^{2+}, Mg^{2+}-free PBS (2.5 ml) was then added to each plate and plates were placed in a 25°C water bath for 5 min. Cells were gently scraped from plates, and cell clusters were separated by trituration with a pipette for 5 to 10 aspirations and ejections.

Aliquots (50 μl) of the suspended cells were added to assay tubes containing drugs and Krebs-HEPES assay buffer in a final volume of 0.5 ml. Competition experiments were conducted with triplicate determinations at each point. After a 10-min preincubation in a 25°C water bath (unless indicated otherwise), [^{3}H]neurotransmitter (20 nM final concentration; [^{3}H]DA, [^{3}H]5-HT, or [^{3}H]NE; 56, 26.9, or 60 Ci/mmol, respectively) was added, and the assay was incubated for 10 min. The reaction was terminated by filtration through Wallace Filtermat A filters, presoaked in 0.05% polyethylenimine, using a Tomtec cell harvester. Scintillation fluid was added to each filtered spot, and radioactivity remaining

on the filters was determined as described above. Specific uptake was defined as the difference in uptake observed in the absence and presence of 5 μM mazindol (HEK-hDAT and –NET) or 5 μM imipramine (HEK-hSERT).

D. DATA ANALYSIS.

Prism software (GraphPad Software, San Diego, CA) was used to analyze all kinetic, saturation, and competition binding data. IC_{50} values were converted to K_i values using the Cheng-Prusoff equation (Cheng Y and Prusoff WH, Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50 per cent binding inhibition (I_{50}) of an enzymatic reaction, *Biochem Pharmacol* 22: 3099-3108 (1973)).

II. RESULTS AND DISCUSSION

The results of this experiment are summarized in Table 1.

Table 1. Activity comparison of (-)-1-(3,4-dlchlorophenyl)-3-azabicyclo[3.1.0]hexane HCl, (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexaneHCl in dopamine, norepinephrine, and serotonin transporter binding and uptake assays using recombinant human receptors.

	Dopamine				**Serotonin**				**Norepinephrine**			
	Binding		Uptake		Binding		Uptake		Binding		Uptake	
Compound	Ki	SEM	IC50	SEM	Ki	SEM	IC50	SEM	Ki	SEM	IC50	SEM
Racemic mixture	186	40	78	15	188	28	13.8	1.5	378	43	20.3	6.1
(+)-enantiomer	213	56	96	20	99	16	12.3	2.8	262	41	22.8	3.3
(-)-enantiomer	222	43	129	15	740	140	133	26	1030	76	103	27

The data in Table 1 show that both (-)-l-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl, (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCI and (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl have similar affinity for the dopamine uptake site as measured by binding and uptake.

Conversely, the data in Table 1 show that (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl have substantially and unexpectedly greater affinity for the serotonin and norepinephrine uptake sites than (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl as measured by both binding and reuptake. With respect to binding to the serotonin uptake site, there is a 3.93 fold difference between (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and a 7.47 fold difference between (-)-1-

(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl. With respect to binding to the norepinephrine uptake site, there is a 2.72 fold difference between (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and a 3.93 fold difference between (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl. With respect to uptake at the serotonin uptake site, there is a 9.63 fold difference between (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and a 10.8 fold difference between (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl. With respect to uptake at the norepinephrine uptake site, there is a 5.07 fold difference between (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and a 4.52 fold difference between (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl.